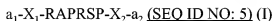


**Amendments to the specification:**

*Rewrite page 7, line 12, through page 8, line 19:*

In addition, the authors of the present invention have demonstrated that the minimum epitope recognized by the antibodies according to the invention has the following sequence: RAPR<sub>76</sub>S<sub>77</sub>P. They have also shown that a successful way of obtaining the antibodies which are the subject of the present invention is to immunize animals with a peptide of general formula:



where

$a_1$  may be H or may represent a function or a chemical group chosen from a thiol, alcohol, aminoxy, primary amine or secondary amine function, an aminocarboxyl group, a biotinyl group and an acetyl group,

$X_1$  represents a peptide sequence of 0 to 3 amino acids, which may or may not be derived from the natural sequence of proBNP(1-108),

$X_2$  represents a peptide sequence of 0 to 8 amino acids, preferably 7 amino acids, which may or may not be derived from the natural sequence of proBNP(1-108),  $a_2$  may represent an OH function, an  $\text{NH}_2$  function, or an alkoxy group.

Similarly, the authors of the present invention have shown that it is possible to obtain the same specific antibodies by immunizing an animal with a peptide comprising the sequence  $\text{RAPR}_{76}\text{S}_{77}\text{P}$  (SEQ ID NO: 5) or with a peptide of formula:



where X may be H or may represent either an acetyl group, or 1 to 3 amino acids not belonging to the sequence of proBNP(1-108), and where Z may represent an OH function, or 1 to 3 amino acids not belonging to the sequence of proBNP(1-108).

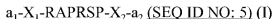
In addition, the authors of the present invention have shown that it is possible to obtain the same specific antibodies by immunizing an animal with a peptide of formula:



where X may be H or may represent either an acetyl group, or 1 to 3 amino acids not belonging to the sequence of proBNP(1-108), and where Z may represent an OH function, or 1 to 3 amino acids not belonging to the sequence of proBNP(1-108).

*Rewrite page 10, line 22, through page 11, line 18:*

A subject of the present invention is also a peptide of formula:



where

a<sub>1</sub> may be H or may represent a function or a chemical group chosen from a thiol, alcohol, aminoxy, primary amine or secondary amine function, an aminocarboxyl group, a biotinyl group and an acetyl group,

X<sub>1</sub> represents a peptide sequence of 0 to 3 amino acids, which may or may not be derived from the natural sequence of proBNP(1-108),

X<sub>2</sub> represents a peptide sequence of 0 to 8 amino acids, preferably 7 amino acids, which may or may not be derived from the natural sequence of proBNP(1-108),

a<sub>2</sub> may represent an OH function, an NH<sub>2</sub> function or an alkoxyl group.

A subject of the present invention is also a peptide of formula: X-Y<sub>70</sub>TLRAPR<sub>76</sub>S<sub>77</sub>PKMVQGS<sub>85</sub>-Z (SEQ ID NO: 4) (II) where X may be H or may represent either an acetyl group, or 1 to 3 amino acids not belonging to the sequence of proBNP(1-108), and where Z may represent an OH function, or 1 to 3 amino acids not belonging to the sequence of proBNP(1-108).

A subject of the present invention is also a peptide of formula: X-Y<sub>70</sub>TLRAPR<sub>76</sub>S<sub>77</sub>PKMVQGS<sub>84</sub>-Z (SEQ ID NO: 108) (III) where X may be H or may represent either an acetyl group, or 1 to 3 amino acids not belonging to the sequence of proBNP(1-108), and where Z may represent an OH function, or 1 to 3 amino acids not belonging to the sequence of proBNP(1-108).

The invention also relates to any peptide containing the sequence X-Y<sub>70</sub>TLRAPR<sub>76</sub>S<sub>77</sub>PKMVQSGS<sub>85</sub>-Z (SEQ ID NO: 4) (II) or the sequence X-Y<sub>70</sub>TLRAPR<sub>76</sub>S<sub>77</sub>PKMVQGS<sub>84</sub>-Z (SEQ ID NO: 108) (III), or one of the abovementioned sequences (II) or (III) in a form which is substituted, conservatively or nonconservatively, at any one of the amino acids of position 70 to position 85 or 84, respectively, on condition that it keeps intact (in particular unsubstituted) the portion RAPR<sub>76</sub>S<sub>77</sub>P.

It is therefore a peptide comprising a sequence derived from the sequence X-Y<sub>70</sub>TLRAPR<sub>76</sub>S<sub>77</sub>PKMVQSGS<sub>85</sub>-Z (SEQ ID NO: 4) (II) or from the sequence X-Y<sub>70</sub>TLRAPR<sub>76</sub>S<sub>77</sub>PKMVQGS<sub>84</sub>-Z (SEQ ID NO: 108) (III) by substitution of one or more among the amino acids Y<sub>70</sub>, T<sub>71</sub>, L<sub>72</sub>, K<sub>79</sub>, M<sub>80</sub>, V<sub>81</sub>, Q<sub>82</sub>, G<sub>83</sub>, S<sub>84</sub> and G<sub>85</sub>, with it being possible for X to be absent or to represent either an NH<sub>2</sub> function, or 1 to 3 amino acids not belonging to the sequence of proBNP(1-108), and it being possible for Z to be absent or to represent either an OH function, or 1 to 3 amino acids not belonging to the sequence of proBNP(1-108).

*Rewrite page 11, line 26, through page 12, line 14:*

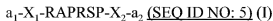
The invention also relates to any peptide containing the sequence X-Y<sub>70</sub>TLRAPR<sub>76</sub>S<sub>77</sub>PKMVQSGS<sub>85</sub>-Z (SEQ ID NO: 4) (II) or the sequence X-Y<sub>70</sub>TLRAPR<sub>76</sub>S<sub>77</sub>PKMVQGS<sub>84</sub>-Z (SEQ ID NO: 108) (III), or one of the abovementioned sequences (II) or (III) in a form which is substituted, conservatively or nonconservatively, at any one

of the amino acids of position 70 to position 85 or 84, respectively, on condition that it keeps intact (in particular unsubstituted) the portion  $\text{RAPR}_{76}\text{S}_{77}\text{P}$  (SEQ ID NO: 5).

It is therefore a peptide comprising a sequence derived from the sequence  $\text{X-Y}_{70}\text{TLRAPR}_{76}\text{S}_{77}\text{PKMVQGS}_{85}\text{-Z}$  (SEQ ID NO: 4) (II) or from the sequence  $\text{X-Y}_{70}\text{TLRAPR}_{76}\text{S}_{77}\text{PKMVQGS}_{84}\text{-Z}$  (SEQ ID NO: 108) (III) by substitution of one or more among the amino acids  $\text{Y}_{70}$ ,  $\text{T}_{71}$ ,  $\text{L}_{72}$ ,  $\text{K}_{79}$ ,  $\text{M}_{80}$ ,  $\text{V}_{81}$ ,  $\text{Q}_{82}$ ,  $\text{G}_{83}$ ,  $\text{S}_{84}$  and  $\text{G}_{85}$ , with it being possible for X to be absent or to represent either an  $\text{NH}_2$  function, or 1 to 3 amino acids not belonging to the sequence of proBNP(1-108), and it being possible for Z to be absent or to represent either an OH function, or 1 to 3 amino acids not belonging to the sequence of proBNP(1-108).

*Rewrite page 12, line 20, through page 14, line 1:*

A subject of the invention is also a method for obtaining anti-proBNP(1-108) antibodies that specifically recognize the sequence  $\text{Y}_{70}\text{TLRAPR}_{76}\text{S}_{77}\text{PKMVQGS}_{85}$  (SEQ ID NO: 4),  $\text{Y}_{70}\text{TLRAPR}_{76}\text{S}_{77}\text{PKMVQGS}_{84}$  (SEQ ID NO: 108) and/or the sequence  $\text{RAPR}_{76}\text{S}_{77}\text{P}$  of proBNP(1-108) with the substantial exclusion of BNP(1-76) and of BNP(77-108), and that have the ability to specifically recognize circulating proBNP(1-108) in human serum or plasma samples, characterized in that an animal is immunized with a peptide of formula:



where  $a_1$ ,  $X_1$ ,  $X_2$  and  $a_2$  have the same meaning as above, and, optionally, in that the antiserum obtained is depleted using the BNP(77-108) peptide and/or the BNP(1-76) peptide. The antibody thus obtained is a monospecific antibody.

A subject of the invention is also a method for obtaining anti-proBNP(1-108) antibodies that specifically recognize the sequence  $Y_{70}TLRAPR_{76}S_{77}PKMVQSGS_{85}$  (SEQ ID NO: 4),  $Y_{70}TLRAPR_{76}S_{77}PKMVQGS_{84}$  (SEQ ID NO: 108) and/or the sequence  $RAPR_{76}S_{77}P$  (SEQ ID NO: 5) of proBNP(1-108) with the substantial exclusion of BNP(1-76) and of BNP(77-108), and that have the ability to specifically recognize circulating proBNP(1-108) in human serum or plasma samples, characterized in that an animal is immunized with a peptide of formula:



or with a peptide of formula  $X-Y_{70}TLRAPR_{76}S_{77}PKMVQGS_{84}-Z$  (SEQ ID NO: 108) (III), where X and Z are as defined above and, optionally, in that the antiserum obtained is depleted using the BNP(77-108) peptide and/or the BNP(1-76) peptide.

A subject of the invention is also a method for obtaining a hybridoma that secretes anti-proBNP(1-108) antibodies that specifically recognize the sequence  $Y_{70}TLRAPR_{76}S_{77}PKMVQSGS_{85}$  (SEQ ID NO: 4),  $Y_{70}TLRAPR_{76}S_{77}PKMVQGS_{84}$  (SEQ ID NO: 108) and/or the sequence  $RAPR_{76}S_{77}P$  of proBNP(1-108) with the substantial exclusion of BNP(1-76) and of BNP(77-108), and that have the ability to specifically recognize circulating

proBNP(1-108) in human serum or plasma samples, characterized in that an animal is immunized with a peptide of formula:

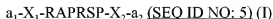


or with a peptide of formula  $X-Y_{70}TLRAPR_{76}S_{77}PKMVQGS_{84}-Z$  (SEQ ID NO: 108) (III),

in a form that is substituted, conservatively or nonconservatively, on condition that it keeps intact (in particular unsubstituted) the portion  $RAPR_{76}S_{77}P$  (SEQ ID NO: 5), where X and Z are as defined above and, optionally, in that the antiserum obtained is depleted using the BNP(77-108) peptide and/or the BNP(1-76) peptide.

*Rewrite the paragraph bridging pages 14 and 15:*

- an animal is immunized with a peptide chosen from the peptides of formulae below:



where  $a_1$ ,  $X_1$ ,  $X_2$  and  $a_2$  have the same meaning as above,



where X and Z have the same meaning as above,



where X and Z have the same meaning as above,



in a form which is substituted, conservatively or nonconservatively, on condition that it keeps intact (in particular unsubstituted) the portion  $\text{RAPR}_{76}\text{S}_{77}\text{P}$ , where X and Z have the same meaning as above,

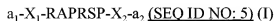


in a form which is substituted, conservatively or nonconservatively, on condition that it keeps intact (in particular unsubstituted) the portion  $\text{RAPR}_{76}\text{S}_{77}\text{P}$  (SEQ ID NO: 5), where X and Z have the same meaning as above,



*Rewrite the paragraph bridging pages 17 and 18:*

Finally, the invention is directed toward a kit for detecting proBNP(1-108) in a biological sample, in particular in a blood, plasma or serum sample, containing, as standard and/or control, a compound containing at least one peptide chosen from the group of peptides of formulae below:



where  $\text{a}_1$ ,  $\text{X}_1$ ,  $\text{X}_2$  and  $\text{a}_2$  have the same meaning as above,



where X and Z have the same meaning as above,





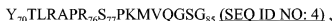
in a form which is substituted, conservatively or nonconservatively, on condition that it keeps intact (in particular unsubstituted) the portion  $\text{RAPR}_{76}\text{S}_{77}\text{P}$  (SEQ ID NO: 5), where X and Z have the same meaning as above,



where X and Z have the same meaning as above



in a form which is substituted, conservatively or nonconservatively, on condition that it keeps intact (in particular unsubstituted) the portion  $\text{RAPR}_{76}\text{S}_{77}\text{P}$  (SEQ ID NO: 5), where X and Z have the same meaning as above,



*Rewrite the paragraph bridging pages 31 and 32:*

For the production of polyclonal antibodies, rabbits (females of the New Zealand strain) were immunized with the peptide  $\text{Cys-YTLRAPRSPKMVQGS-NH}_2$  (SEQ ID No. 16) coupled to KLH according to example 2. For the first injection, an emulsion of 1.5 ml of KLH-coupled peptide with 1.5 ml of complete Freund's adjuvant (Sigma # F-5881) is prepared and 1 ml of this latter emulsion (i.e. 200 µg of peptide) is injected intradermally into each of the rabbits. Two boosters are given, 20 days apart, by intradermal injection of 1 ml of an emulsion of KLH-coupled peptide (i.e. 200 µg of peptide) with incomplete Freund's adjuvant (Sigma # F-5506). Twenty days after the second

booster, a third booster is given in the same way as the previous boosters, but by subcutaneous injection. Twenty days after the latter booster, and after evaluation of the antibody titer obtained, the rabbits are bled. More particularly, the polyclonal antibodies from the rabbits identified by the numbers #046 805 and 046 832, obtained by immunization with the peptide ~~C-YTLRAPRSPKMVQGS-NH<sub>2</sub>~~, C-YTLRAPRSPKMVOGSG-NH<sub>2</sub> (SEQ ID No. 16) coupled to KLH, and from the rabbit identified by # L01235, obtained by immunization with the peptide C-YTLRAPRSPKMVQGS-NH<sub>2</sub> (SEQ ID No. 109) coupled to KLH, were used for the rest of the studies.